Translation

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference BLOjp64441EX	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/FR00/00613	International filing date (*day/month/year*) 14 March 2000 (14.03.00)	Priority date (*day/month/year*) 15 March 1999 (15.03.99)
International Patent Classification (IPC) or national classification and IPC G01N 33/74, 33/566, 33/573		
Applicant CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE-CNRS		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☒ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
04 October 2000 (04.10.00)	22 June 2001 (22.06.2001)
Name and mailing address of the IPEA/EP Facsimile No.	Authorized officer Telephone No.

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International application No.
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

I. Basis of the report

1. This report has been drawn on the basis of (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

☐ the international application as originally filed.

☒ the description, pages 1-11, as originally filed,
pages _____, filed with the demand,
pages _____, filed with the letter of _____,
pages _____, filed with the letter of _____.

☒ the claims, Nos. 1-7, as originally filed,
Nos. _____, as amended under Article 19,
Nos. _____, filed with the demand,
Nos. _____, filed with the letter of _____,
Nos. _____, filed with the letter of _____.

☐ the drawings, sheets/fig 1/7-7/7, as originally filed,
sheets/fig _____, filed with the demand,
sheets/fig _____, filed with the letter of _____,
sheets/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/fig _____

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

4. Additional observations, if necessary:

Sequence listing part of the application, pages: 1-16 as originally filed

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: I I .

The priority date of the present application is validly claimed as regards the use of the insulin receptor and of fragments consisting of the Grb14 or Grb10 PIR or PIR-SH2 domains (cf. Examples 2 and 3, Figures 7 and 8 of the priority document).

However, the priority date of the present application is not validly claimed as regards the use of a fragment consisting of the Grb7 PIR or PIR-SH2 domain. The priority document only describes the use of the whole Grb7 protein (cf. Example 1).

The priority date of the present application is validly claimed as regards sequences SEQ ID NO. 2, 6 and 14, and the use thereof. Said sequences correspond to SEQ ID NO. 1, 2 and 3 of Figure 4 of the priority document.

The priority date of the present application is not validly claimed as regards sequences SEQ ID NO. 1, 3-5, 7-13 and 15-28, as well as the use thereof.

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V. **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-7	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1-7	NO
Industrial applicability (IA)	Claims	1-7	YES
	Claims		NO

2. Citations and explanations

Reference is made to the following documents:

D1: US-A-5 840 536

D2: US-A-5 726 027

D3: WO 98 01475 A

D4: A KASUS-JACOBI, D PERDEREAU, C AUZAN, E CLAUSER, E VAN OBBERGHEN, F MAUVAIS-JARVIS, J GIRARD, A-F BURNOL: 'Identification of the Rat Adapter Grb14 as an Inhibitor of Insulin Actions', JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 273, no. 40, 2 October 1998 (1998-10-02), pages 26026-26035, XP002124253, cited in the application.

D5: W HE, D W ROSE, J M OLEFSKY, T A GUSTAFSON: 'Grb10 interacts Differentially with the Insulin Receptor, Insulin-like Growth Factor I Receptor, and Epidermal Growth Factor Receptor via the Grb10 Src Homology (SH2) Domain and a Second Novel Domain Located between the Pleckstrin Homology and SH2 Domains', JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 273, no. 12, 20 March 1998 (1998-03-20), pages 6860-6867, XP002124256, cited in the application.

D6: US-A-5 889 150.

1. Document D2 (cf. abstract and claim) describes a method for screening molecules affecting the binding of protein tyrosine phosphatase (PTP1B) with the activated insulin receptor.

The subject matter of Claims 1 and 3 of the present application differs from D2 in that a fragment consisting of the PIR or PIR-SH2 domain of a protein of the Grb7 family is used instead of PTP1B. The method of Claim 3 further differs therefrom in that the modulation of the insulin receptor tyrosine kinase activity is determined.

As for the screening methods of documents D1 and D3, these use GrbIR-1 (Grb10 isoform) and cellular effectors ("cellular binding partner") which do not include the insulin receptor (cf. D1, Column 3, lines 11-54; Column 10, lines 42-65; Column 12, lines 8-49; and D3, Claims 17-20; page 19, lines 8-11 and page 22, lines 22-24; line 2). D1 and D3 do not mention the PIR or PIR-SH2 domains.
The subject matter of Claim 1 and 3 of the present application therefore differs from D1 in that a fragment consisting of the PIR or PIR-SH2 domain of a protein of the Grb7 family is used instead of GrbIR-1. The method of Claim 3 further differs therefrom in that the insulin receptor is used.

The subject matter of Claims 1 and 3 is therefore novel (PCT Article 33(2)).

2. The problem that Claim 1 proposes to solve can be

considered to be that of using other compounds to screen molecules for treating insulin-mediated disorders.

The solution proposed in said claim is not considered to be inventive (PCT Article 33(3)) for the following reasons:

Documents D4 (summary, Figure 2A and discussion) and D5 (summary, Figures 2, 3 and 7; PIR is here designated BPS) demonstrate that the PIR and PIR-SH2 domains are responsible for the interaction between Grb14 and/or Grb10 and the insulin receptor, and that a 43 aa region is highly conserved within Grb14, Grb7 and Grb10 (cf. e.g. D4, page 26030, right-hand column, 3rd paragraph).

The use of the PIR or PIR-SH2 domains for screening molecules for treating insulin-mediated disorders therefore appears to be an obvious and desirable measure for a person skilled in the art.

The sequences of Claim 2 (see also page 4, line 32 to page 5, line 1 of the present application) do not involve an inventive step, since the PIR, PIR-SH2 domains and the conserved 43 aa region had been identified and the function thereof was known in the prior art (D4, D5, supra, infra and in particular Figure 2 of D5; D4, page 26030, Column 2, 3rd paragraph).

3. The problem that Claim 3 aims to solve can be considered to be that of providing a method for identifying molecules capable of modulating insulin receptor tyrosine kinase activity.

The solution proposed in said claim is not considered inventive (PCT Article 33(3)) for the following reasons:

D4 and D5, which are written by two different research teams, suggest that the interaction between the insulin receptor and Grb10 or Grb14 modulates the tyrosine kinase activity of said receptor (cf. the last four paragraphs of D4 and the last paragraph of D5). In view of the above arguments, it appears obvious and desirable for a person skilled in the art to use the activated insulin receptor, the PIR domain, the conserved portion thereof or PIR-Sh2 and to measure the tyrosine kinase activity of said receptor.

Dependent Claims 4 and 5 do not contain any feature defining subject matter which meets the PCT requirements with respect to inventive step (Claim 4: cf. last paragraph of point 2 above; Claim 5; since the fragment/receptor interaction is indeed characterised in the prior art, this preselection step appears to be an ordinary measure for a person skilled in the art).

4. It appears that the subject matter of Claim 6 is not described in the prior art. Therefore, said subject matter is novel (PCT Article 33(2)).

Screening of agonists and antagonists of a protein of the Grb7 family capable of modulating insulin receptor tyrosine kinase activity does not appear to be inventive (Claims 1-5, cf. points 2 and 3 above). A compound capable of binding to PIR or PIR-SH2 and

of inhibiting the tyrosine kinase activity of the receptor is therefore one of the molecules sought. It is obvious that the aim of such a screening is, primarily, to identify molecules useful for preparing a drug for treating insulin-mediated disorders.

Therefore, it appears that the subject matter of Claims 6 and 7 does not involve an inventive step.

5. Note: D4 and D5 respectively describe the interaction between Grb14 and Grb10 and the insulin receptor. In view of the known homology with Grb7 (in particular that of the PIR and PIR-SH2 domains and of the highly conserved region), a person skilled in the art would be able to extrapolate the results obtained with Grb14 and Grb10 (prior art) to Grb7 or the family of Grb7 proteins with a reasonable expectation of success.

6. The priority date is not validly claimed as regards certain aspects of the present application (cf. Box II above).

The P,X document (D6) cited in the search report therefore forms part of the prior art for said aspects.

Nevertheless, D6 (Example X, Columns 51-53) does not mention or suggest in an obvious manner the use
- of fragments consisting of the PIR or PIR-SH2 domain of a protein of the Grb7 protein family, nor that
- of the insulin receptor.

D6 therefore appears to be prejudicial to the novelty and inventive step of the subject matter of the claims of the present application.

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

Contrary to the requirements of PCT Rule 5.1(a)(ii), the description does not outline the relevant prior art set forth in document D2 and does not cite this document.

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The expression "determining the effect of the molecule", point 6) of Claim 5, is vague and ambiguous, and casts doubt as to the meaning of the technical features to which it refers.

Therefore, the subject matter of said claim has not been clearly defined (PCT Article 6).

The insertion of the phrase "inhibiting or stimulating fragment/receptor interaction" (cf. page 6, lines 31-32, but without the parentheses), would rectify this lack of clarity.